REMARKS

Status of the claims

Claims 1-17, 21 and 22 are pending in the application. Claims 1-17, 21 and 22 are rejected. By this amendment, claims 2-5 and 11-17 are amended and new claim 23 is added. No new matter is added by these amendments. Support for amended claims 4, 10 and new claim 23 is provided in the specification and pending claims, *see, e.g.*, Example 1 (disclosing preparation of mammalian packaging cell using a single plasmid comprising AAV rep and cap genes). Applicant also notes that claims 16 and 17 have been amended to remove the step of providing an AAV packaging cell of claim 1 and 10, respectively. Clause (a) of claims 16 and 17 (as amended) now recite that helper virus is introduced into the AAV packaging cell of claim 1 and 10, respectively.

With respect to all amendments and cancelled claims, Applicant has not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicant reserves the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional application. Attached hereto is a marked up version of the changes made to the specification by the current amendment with additions underlined and deletions bracketed. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**".

Information Disclosure Statement

Applicant acknowledges the Examiner's helpful comments regarding the IDS filed on September 20, 2001. Submitted herewith is a Supplemental IDS with copies of references 39-41 and 43-45, which the Examiner noted were missing from the IDS submitted in the parent application. Applicant also notes that the 1449 submitted herewith now lists the correct date for

document no. 15. Applicant respectfully requests that the Examiner initial and return the enclosed Form 1449.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1-5 and 10-17 are rejected under 35 U.S.C. 112, second paragraph, as being allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant traverses this rejection.

A. Claims 1-5 and 10-17 are rejected as allegedly indefinite because the claims allegedly "do not define whether the p5 promoter in the genome of the cell was modified before it was in the cell or that the p5 promoter function will be replaced by adding a plasmid with an AAV rep gene operably linked to a helper virus-inducible heterologous promoter." *See* Office Action, page 3. Applicant traverses this rejection.

As a preliminary matter, Applicant points out that the p5 promoter is an AAV promoter located in the ITR region of AAV, which promoter directs transcription of AAV rep genes. *See, e.g.* specification at page 4, lines 1-3; lines 12-24. Thus, Applicant submits that it is clear that the phrase "wherein p5 promoter function has been replaced by the helper virus-inducible heterologous promoter" refers to the replacement of the AAV p5 promoter function with a helper virus-inducible promoter, such that the stably integrated AAV rep gene is operably linked to a helper virus-inducible promoter, not the p5 promoter. Applicant notes that the phrase was added during the prosecution of the parent case in order to clarify precisely this point: that the p5 promoter function is replaced by the heterologous promoter.

To the extent that the Examiner is asserting that the claims are indefinite because they do not recite *when* the p5 promoter is replaced by the helper virus-inducible promoter (i.e., either "before it was in the cell" or "by adding a plasmid", as the Examiner seems to state in the rejection, *see* Office Action, page 3, Applicant submits that there is no basis under the law for requiring that the claim specify when the p5 promoter is replaced by the helper virus inducible promoter. Even so, Applicant points out that claims 1 and 10 recite that "p5 promoter function

has been replaced by the helper virus-inducible heterologous promoter", thus clearly indicating that the mammalian cell of clause (a) comprises a stably integrated AAV rep gene operably linked to a helper virus-inducible promoter, which helper virus-inducible promoter has replaced p5 promoter function. Accordingly, Applicant submits that these claims are clear. Withdrawal of this rejection is respectfully requested.

B. Claims 4 and 13 are rejected as indefinite for allegedly failing to further limit claims 1 and 10, respectively. Applicant traverses this rejection. Applicant notes that claims 4 and 13 require that the mammalian cell comprises the combined rep and cap genes. By contrast, independent claims 1 and 10 state that the mammalian cell comprises a stably integrated AAV cap gene and a stably integrated AAV rep gene. Claims 16 and 17 do not require that the rep and cap genes are combined. Accordingly, Applicant submits that claims 4 and 13 do further limit independent claims 1 and 10, respectively. However, to clarify these claims, claims 4 and 13 have been amended to recite that have been amended to require that the AAV packaging cell is prepared using a single plasmid, said plasmid comprising AAV rep gene operably linked to a heterologous promoter and AAV cap gene operably linked to a promoter, wherein p5 promoter function has been replaced by a heterologous promoter. New claim 23 also recites this language. Applicant believes that these amendments address the Examiner's concerns, and withdrawal of this rejection is respectfully requested.

C. Claims 2-5 and 11-17 are rejected as allegedly indefinite for reciting "a" and "an" instead of "the", as detailed in the Office Action at page 4. Although Applicant respectfully submits this format for claims is proper, claims 2-5 and 11-17 have been amended to incorporate the Examiner's suggestions. These amendments are non-limiting. Withdrawal of this rejection is respectfully requested.

Rejections under 35 U.S.C. § 102(e)

Claims 1-4, 6-8, 10-13, 15-17, and 21-22 are rejected under 35 U.S.C. 102(e) as allegedly anticipated by Flotte et al. (US Patent No. 5,658,776). Applicant respectfully traverses this rejection.

As a preliminary matter, Applicant notes that the present application was filed as a continuation application on December 6, 2000, and thus the changes under the AIPA do apply to the examination of this application, contrary to the Examiner's statement on page 4 of the Office Action. *See* MPEP Section 2136.

Turning to the substance of the rejection, Flotte does not anticipate the rejected claims because Flotte does not teach each and every limitation of the rejected claims. The Examiner cites Flotte as disclosing a "stable cell line containing an AAV CFTR vector and a pSVNeo plasmid" and that "the pSVneo plasmid contains a heterologous promoter (HIV-LTR) operably linked to the rep and cap gene of AAV (Figure 2)." *See* Office Action, page 3. By contrast, Flotte discloses cell populations containing integrated but rescuable copies of the AAV-neo vector genome. *See* col. 18, lines 44-50; col. 19, lines 4-10. These stable vector lines are then transfected with pHIVrep/p40cap to produce rAAV vector stocks. These cell lines are not characterized by Flotte as stably expressing rep and cap. Rather, they stably contain the AAV-neo vector genome. Flotte describes packaging experiments in which adenovirus-infected 293 cells are *transiently* transfected with both rAAV (pTRF42) and packaging plasmid (pHIVrep/p40cap). col. 18-19, *e.g.*, col. 19, lines 4-10. Nowhere does Flotte describe stable integration of AAV rep and cap genes; and, as noted above, claims 1 requires that the AAV rep and cap genes be stably integrated.

Experiments in Flotte et al. involving a packaging construct in which rep was placed under the control of the HIV promoter (i.e. pHIVrep/p40cap) were also referred to by the Office, but are likewise distinguishable. Again, there is no teaching of stably integrating the AAV rep and cap genes.

In summary, the disclosure of Flotte does not meet the limitations of the claimed invention. Applicant submits that the present invention, as described and claimed, distinguishes over Flotte at least because the cell of step (a) of claim 1 comprises a stably integrated AAV cap gene and a stably integrated AAV rep gene. Withdrawal of this rejection is respectfully requested.

Rejections under 35 U.S.C. § 103(a)

Yang e al. in view of Johnson et al.

Claims 1-17 and 21-22 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Yang et al. (*J. Virol* (1994) 68:4847-4856) taken with Johnson (US Patent No. 5658785). The Examiner cites Johnson as allegedly disclosing packaging cell lines comprising stably integrated rep-cap sequences. Yang is cited as allegedly disclosing "inducible Rep-expressing cell lines under the control of the mouse metallothionein I promoter", and "use of the adenovirus type 2 (helper virus) for co-infection." *See* Office Action, page 6. The Examiner further notes that Yang does not teach a rep-expressing cell line also comprising a stable integrated cap gene. According to the Examiner, "one of skill in the art would be motivated to include cap in a rep-expressing cell line based on the art-recognized goal to provide more efficient methods of packaging rAAV by eliminating co-transfection steps." *Id.*

As a preliminary matter, Applicant disagrees with the Examiner's characterization of the present claims as pertaining to "stable cell lines comprising both inducible rep and cap sequences." *See* Office Action, page 6. Applicant notes that the present claims recite a stably integrated AAV cap gene operably linked to a promoter, and a stably integrated AAV rep gene operably linked to a helper virus-inducible promoter." Thus, the present claims do not require that the AAV cap gene is operably linked to an inducible promoter, contrary to the Examiner's statement in the Office Action.

Turning to the substance of the rejection, Applicant respectfully traverses this rejection. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, the prior art reference(s) must teach or suggest all the claim limitations. Second, there must be some suggestion or motivation to modify the reference or to combine reference teachings. Third, there must be a reasonable expectation of success. *See* M.P.E.P. § 2143. All three criteria must be met. The rejection of claimed subject matter as obvious in view of a combination of prior art reference requires consideration of whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, and whether the prior art would also have revealed that such persons would have reasonable success. Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the Applicant's disclosure. *See In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991).

Applicant respectfully submits that the Examiner has not made a *prima facie* case of obviousness because the cited references do not teach or suggest all of the limitations of the claims. Moreover, the Examiner has not shown a suggestion or motivation to combine the Yang reference with the Johnson reference, nor has the Examiner shown that there is a reasonable expectation of success.

The Examiner has not made a *prima facie* case of obviousness because neither Johnson nor Yang expressly teach or suggest a stably integrated rep gene operably linked to a helper virus-inducible heterologous promoter. As noted by the Examiner, Yang discloses generation of inducible Rep-expressing cell lines comprising the rep gene under control of the mMT-1 promoter. However, Yang teaches that the mMT-1 promoter is a metal-inducible promoter (see, e.g., page 4848, first column). Yang does not state anywhere in the paper that this promoter is helper virus-inducible. Moreover, Yang's experiments fail to teach or suggest that mMT-1 promoter is helper-virus inducible. For example, in the absence of heavy metal induction, but in the presence of Ad virus co-infection, Yang did not observe rep expression or a variety of other

rep-mediated functions. *See, e.g.*, Figs. 2-4. Thus, it is evident that Yang does not expressly teach or suggest that mMT-1 promoter is a helper-virus inducible promoter.

At best, Yang et al. *inherently* disclose a stably integrated rep gene operably linked to a helper virus-inducible heterologous promoter. However, it is well-established under the law that an inherent teaching in a reference may not be used to create a prima face case of obviousness. In *In re Rickaert*, the Federal Circuit reversed an obviousness rejection based on the combination of two prior art rejections, where one of the limitations was allegedly inherently taught by one of the references. *See In re Rickjaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). The court held that a prima facie case of obviousness had not been established because "[t]hat that is inherent is not necessarily known. Obviousness cannot be predicated on what is unknown. Such a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection." *Id.* (citations omitted); *see also In re Spormann,* 150 USPQ 449, 452 (CCPA 1966). In a similar case, the court reversed an obviousness rejection based on the combination of two references, stating "a retrospective view of inherency is not a substitute for some teaching or suggestion which supports the selection and use of the various elements in the particular claimed combination. It is well established that in deciding that a novel combination would have been obvious, there must be supporting teaching in the prior art. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." *In re Newell*, 13 USPQ2d 1248, 1250 (Fed. Cir. 1989). Thus, established caselaw states that a *prima facie* case of obviousness cannot rely on an alleged inherent disclosure of a limitation. Accordingly, a *prima facie* case of obviousness has not been made. Withdrawal of this rejection is respectfully requested.

Applicant further submits that one of skill in the art would not be motivated to combine Yang with Johnson, nor would there be a reasonable expectation of success. The Examiner states that "one of skill in the art would be motivated to include cap in a rep-expressing cell line based on the art-recognized goal to provide more efficient methods of packaging rAAV by

eliminating co-transfection steps." *See* Office Action, page 6. Applicant points out, however, that the Yang et al. reference teaches away from the use of inducible Rep-expressing cell lines comprising the rep gene under control of the mMT-1 promoter because Yang teaches that the mMT-1/rep expressing cells progress through DNA synthesis at a slower rate than control cells, even in the absence of heavy metals.[1] *See* Yang, p.4856, second full paragraph. Yang also observed that efficiency of colony formation and growth rate were slower in rep-producing cells (even in the absence of metal induction). *See* page 4855, first paragraph. Yang further noted that they had poor success as preparing the rep-producing cell lines, as follows:

> [I]t has been difficult to obtain cell lines that either constitutively or inducibly express Rep proteins because of the inhibitory effects that the AAV rep gene exerts on heterologous gene expression and cellular proliferation. After multiple DNA transfection experiments using pSV2neo and [mMT1-rep], we were able to generate 20 cell lines, only one of which was capable of expression rep protein upon induction with heavy metals.
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> Yang et al., p4854.

Applicant submits that one skilled in the art would not select cells that proceed through DNA synthesis slowly, exhibit slow growth, and were difficult to generate, in order to generate a more efficient packaging system.

Moreover, there is no reasonable expectation of success in the combination of Yang and Johnson. As noted above, Yang's cells grew slowly, were difficult to produce, and apparently proceed slowly through DNA synthesis. In view of this teaching, one skilled in the art would not be motivated to make mammalian cells comprising stably integrated AAV cap gene and stably integrated rep gene, wherein the rep gene is operably linked to a heterologous promoter. Accordingly, a *prima facie* case of obviousness has not been made, because Yang teaches away

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[1] A reference teaches away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant. *See In re Gurly*, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). If a reference teaches away from the claimed invention, that finding alone can defeat a *prima facie* case of obviousness. *See Winner Int'l Royalty Corp. v. Wang*, 53 USPQ2d 1580 (Fed. Cir. 2000).

the claimed invention. In view of this evidence, and based on the arguments made above, Applicant respectfully requests withdrawal of this rejection.

Thus, because of lack of motivation to combine as well as lack of reasonable expectation of success (either of which alone is sufficient to preclude obviousness), it is evident that a *prima facie* case of obviousness has not been made. Applicant respectfully request withdrawal of this rejection.

Flotte et al. in view of Tempe et al.

Claims 1-17 and 21-22 are rejected under 35 U.S.C. 103(a) as allegedly unpatentable over Flotte et al. (US Patent No. 5,658,776) taken with Trempe at al. (US Patent No. 5,837,484) Applicant respectfully traverse this rejection.

The Examiner has not made a *prima facie* case of obviousness because the cited references do not teach or suggest each and every limitation of the rejected claims. As noted above, Flotte does not teach a stably integrated AAV cap gene and a stably integrated AAV rep gene. Trempe does not remedy Flotte's deficiencies. Specifically, there is no teaching or suggestion in Trempe of having an integrated AAV cap gene, or of any advantages conferred by having both AAV rep and cap genes integrated in a mammalian packaging cell. see U.S. Patent No. 5,837,484, column 7, lines 6-13. Thus, a *prima facie* case of obviousness has not been made. Withdrawal of this rejection is respectfully requested.

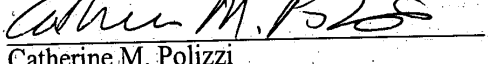
CONCLUSION

Applicant believe that the claims are in condition for allowance. Early notification to that effect is earnestly solicited. Should Examiner Whiteman find any issues outstanding after consideration of this Amendment, he is respectfully requested to contact the undersigned at (650) 813-5651.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicant petition for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 226272001403. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: _August 13, 2002

By: 

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"VERSION WITH MARKINGS TO SHOW CHANGES MADE"

2. (Amended) [A]The method according to claim 1, wherein said helper virus is an adenovirus.

3. (Amended) [A]The method according to claim 1, wherein said packaging cell grows at least one half as rapidly as parental-type cells that do not contain an AAV rep gene, and wherein said packaging cell when used to package rAAV vectors produces at least 100 rAAV particles/cell.

4. (Amended) [A]The method according to any of claims 1-3, wherein said mammalian cell of step (a) is prepared using a single plasmid, said plasmid comprising AAV rep gene operably linked to a heterologous promoter and AAV cap gene operably linked to a promoter, wherein [comprises the combined rep and cap genes of AAV in which the]p5 promoter function has been replaced by a heterologous promoter.

5. (Amended) [A]The method according to claim 4, wherein said heterologous promoter is a mouse metallothionein I (mMT-I) promoter.

11. (Amended) [An]The AAV packaging cell of claim 10, wherein said helper-virus-inducible expression of said stably integrated AAV rep gene is inducible by adenovirus.

12. (Amended) [An]The AAV packaging cell of claim 10, wherein said packaging cell grows at least one half as rapidly as parental-type cells that do not contain an AAV rep gene, and wherein said packaging cell when used to package rAAV vectors produces at least 100 rAAV particles/cell.

13. (Amended) [An]The AAV packaging cell of any of claims 10-12, wherein said cell is prepared using a single plasmid, said plasmid comprising AAV rep gene operably linked to a heterologous promoter and AAV cap gene operably linked to a promoter, wherein [comprises the combined rep and cap genes of AAV in which the]p5 promoter function has been replaced by a heterologous promoter.

14. (Amended) [An]The AAV packaging cell of claim 13, wherein said heterologous promoter is a mouse metallothionein I (mMT-I) promoter.

15. (Amended) [An]The AAV packaging cell of claim 10, further comprising a stably integrated recombinant AAV (rAAV) vector, said vector comprising a polynucleotide sequence of interest located between two AAV inverted terminal repeat (ITR) regions, wherein said polynucleotide is operably linked to a promoter.

16. (Amended) A method of packaging a recombinant AAV vector, comprising the steps of:

(a) [providing an AAV packaging cell of claim 10;

(b)] introducing a recombinant AAV (rAAV) vector into the AAV packaging cell of claim 10, said vector comprising a polynucleotide sequence of interest located between two AAV inverted terminal repeat (ITR) regions, wherein said polynucleotide is operably linked to a promoter;

[(c)](b) introducing a helper virus; and

[(d)](c) incubating the cell under conditions suitable for replication and packaging of AAV such that said rAAV vector is packaged.

17. (Amended) A method of packaging a recombinant AAV vector, comprising the steps of:

(a) [providing an AAV packaging cell of claim 15 which comprises a stably integrated rAAV vector comprising a polynucleotide of interest operably linked to a promoter;

(b)] introducing a helper virus into an AAV packaging cell of claim 15 which comprises a stably integrated rAAV vector comprising a polynucleotide of interest operably linked to a promoter; and

[(c)](b) incubating the cell under conditions suitable for replication and packaging of AAV such that said rAAV vector is packaged.

Please add new claim 23.